REMARKS

It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims remaining be allowed.

Interview Summary

Applicants wish to thank Examiner Harris for extending the courtesy of discussing this application with inventor Matthew Coffey and Applicants' representatives Mary Ann Dillahunty and the undersigned in a personal interview on February 17, 2005. No exhibit was presented.

The two rejections under 35 U.S.C. §112 were discussed, and all the pending claims were discussed in view of the cited references. Applicants pointed out that in view of knowledge available in the art, hematopoietic stem cells harvested from blood would have been expected to have an activated ras pathway. Therefore, a skilled artisan would not have been motivated to treat such cells with reovirus, as required by the current claims. The Examiner asked Applicants to submit the argument and evidence in writing. Applicants submit that the amendments and arguments presented herein are made in accordance with these discussions, and the currently pending claims are in condition for allowance.

Claim Amendments

Claims 39, 40, 45, 46, 52 and 53 have been canceled without prejudice or disclaimer.

Claim 18 has been amended to remove the recitation "wherein said transplantation is autologous", which was added previously during prosecution. Support for this amendment can be found, for example, in the original claim 17.

Claims 38, 44 and 50 have been amended by incorporating the recitation from dependent claims 40, 46, and 53 that the hematopoietic cells are harvested from blood. In accordance with this amendment, claims 39, 40, 45, 46, 52 and 53 have been canceled.

Claim 50 has also been amended to recite "without altering" the ability of the hematopoietic cells to differentiate into each and every hematopoietic lineage for additional clarity.

No new matter has been added by these amendments. The Examiner is hereby requested to enter these amendments.

Applicants submit that all claim amendments presented herein or previously are made solely in the interest of expediting allowance of the claims and should not be interpreted as acquiescence to any rejections or ground of unpatentability. Applicants reserve the right to file at least one continuing application to pursue any subject matter that is canceled or removed from prosecution due to the amendments.

Rejections Under 35 U.S.C. §112, First Paragraph (Paragraphs 3 and 4 of the Office Action)

Claims 50-59 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing new matter. The Office Action states that Applicants cited as support original claims 17 and 2, as well as page 50, lines 6-15, but no support was found with regard to "to result in oncolysis of ras-mediated neoplastic cells under conditions that does not alter the ability of the hematopoietic stem cells to differentiate into each and every hematopoietic lineage." Applicants submit that "page 15, lines 6-15" should have been cited instead of "page 50, lines 6-15", and regret any inconvenience this typographical error has caused.

At page 15, lines 6-15, the specification first states:

> In order for reovirus to be useful in purging hematopoietic stem cell in high dose chemotherapy treatments, it is essential that the reovirus treatment does not alter the ability of stem cells to differentiate into each and every hematopoietic lineage to reconstitute the whole hematopoietic system.

The specification then discusses experimental results that indicate that reovirus treatment does not alter the ability of stem cells to differentiate into each and every hematopoietic lineage. Thus, the recitation at issue is supported by the specification.

Accordingly, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. §112, Second Paragraph (Paragraphs 5 and 6 of the Office Action)

Claims 50-59 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for reciting "under conditions". Since claim 50, as amended, no longer recites "under conditions," this rejection is now moot.

Accordingly, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. §103

A. Gulati in view of Coffey et al. and Freshney (Paragraph 7 of the Office Action)

The rejection of claims 18, 19, 25, 27-32, 34-40, 43-46, 49 and 50-59 under 35 U.S.C. §103(a) over Gulati (J. Hematotherapy 2:467-471, 1993), in view of Coffey *et al.* (Science 282:1332-1334, 1998) and Freshney (Culture of Animal Cells: A Manual of Basic Technique, second edition, New York, NY 1987), is respectfully traversed for the reasons set forth below.

Claims 18 and 19 are directed to methods of preparing a cellular composition for transplantation into a recipient, comprising contacting the composition with a reovirus *ex vivo* to result in oncolysis of ras-mediated neoplastic cells. The cellular composition may be hematopoietic cells harvested from blood. Claim 50 is directed to a method of preparing a cellular composition that comprises hematopoietic stem cells harvested from blood for transplantation into a recipient, comprising contacting the cellular composition with a reovirus ex vivo to result in oncolysis of ras-mediated neoplastic cells without altering the ability of the hematopoietic cells to differentiate into each and every hematopoietic lineage.

Gulati teaches that autologous stem cell transplantation has improved the long-term disease-free survival of patients with various malignancies, and purging of the stem cell graft proved to have clinical benefit. Gulati also teaches that various purging techniques are available, including positive and negative selections. Coffey *et al.* teach that reovirus infects cells with an activated Ras signaling pathway, and that administration of reovirus to an animal bearing a tumor with an

activated Ras signaling pathway resulted in regression of the tumor. Freshney teaches a method for freezing animal cell lines by suspending the cells in culture medium containing a preservative, and freezing the resultant mixture at a low temperature.

The Office Action takes the position that Gulati teaches purging hematopoietic stem cells with negative selection, thus a skilled artisan allegedly would have been motivated to combine Gulati with Coffey et al. and arrive at the use of reovirus to purge hematopoietic stem cells. However, as explained in the Declaration Of Matthew C. Coffey, Ph.D. Under 37 C.F.R. § 1.132 ("Dr. Coffey's Declaration", submitted herewith) and articulated below, a skilled artisan in fact would not have been so motivated.

Dr. Coffey points out in his declaration that it has been a routine practice for many years to harvest hematopoietic stem cells from blood as "peripheral blood progenitor cells (PBPC)" (Paragraph 6 of Dr. Coffey's Declaration). Dr. Coffey further explains that harvesting PBPC involves using granulocyte colony stimulating factor (G-CSF) or granulocyte macrophage colony stimulating factor (GM-CSF) to mobilize progenitor cells from bone marrow to blood (Paragraph 7 of Dr. Coffey's Declaration):

> A key concept in the use of PBPC transplantation is the fact that hematopoietic cytokines can mobilize a large number of progenitor cells into the circulation (reviewed in Reddy). Granulocyte colony stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF) are the most commonly used factors for immobilization, and G-CSF was found to be more effective than GM-CSF (page 64, right column, first paragraph under "Hematopoietic cytokines" of Exhibit C). For example, allogeneic transplant donors are generally mobilized with daily subcutaneous injections of 10μg/kg of G-CSF for 5 days (abstract of Exhibit C).

Dr. Coffey further points out that it has been known in the art that both G-CSF and GM-CSF stimulate proliferation of hematopoietic cells by activating the ras pathway (Paragraph 8 of Dr. Coffey's Declaration). Since PBPCs are typically collected using G-CSF and/or GM-CSF, in Dr. Coffey's opinion, a skilled artisan would expect PBPCs to have an activated ras pathway and be prone to reovirus infection, thus the skilled artisan would not have been motivated to treat PBPCs with reovirus. *Id.*

Accordingly, it is surprising to a skilled artisan that reovirus can selectively kill ras-mediated neoplastic cells when such cells are mixed with PBPCs, and that reovirus treatment neither inhibits cell proliferation nor alters differentiation potential of PBPCs (Paragraph 9 of Dr. Coffey's Declaration). Dr. Coffey thus concludes that the present invention was not obvious to skilled artisans at the time the application as filed (Paragraphs 5 and 9 of Dr. Coffey's Declaration).

Thus, the claimed invention is not obvious in view of the cited references, and withdrawal of this rejection is respectfully requested.

B. The other rejections under 35 U.S.C. §103 (Paragraphs 8-10 of the Office Action)

Various claims of the present application also stand rejected under 35 U.S.C. §103(a) over the following references:

- Gulati in view of Coffey *et al.* and U.S. Patent No. 6,136,307 ("the '307 patent");
- Gulati in view of Coffey *et al.*, U.S. Patent No. 5,861,159 ("the '159 patent"), Freshney and the '307 patent;
- Nordon *et al.* (Artificial Organs 20(5):396-402, 1996), in view of Coffey *et al.* and the '307 patent.

These rejections are respectfully traversed for the same reasons discussed above. Briefly, according to Dr. Coffey's Declaration, hematopoietic stem cells harvested from blood would be considered by skilled artisans as ras-activated cells. Accordingly, a skilled artisan would not have been motivated to treat such cells with reovirus. It is surprising that reovirus can selectively kill ras-mediated neoplastic cells that are mixed with PBPCs, and that reovirus treatment neither inhibits cell proliferation nor alters differentiation potential of PBPCs. Thus, in Dr. Coffey's opinion, the current claims are not obvious in view of the cited references.

Accordingly, withdrawal of these rejections is respectfully requested.

Conclusions

For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's objections and rejections are hereby requested. Allowance of the claims remaining in this application is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at (650) 839-5044.

Enclosed is a $510.00 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: Mar. 22, 2005

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